

Pertussis in Young Infants – Guidance for Clinicians

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Pertussis in the first three months of life is frequently severe and often fatal.^{1,2} In California approximately three infant deaths due to *Bordetella pertussis* infections are reported each year during non-peak years and it is likely that other deaths resulting from *B. pertussis* infection occur but the etiology is attributed to other causes.

The severity of pertussis and the rapidity of its progression in young infants are affected by a number of factors such as the presence of transplacentally acquired maternal antibodies to *B. pertussis*, the infectious dose of bacteria that the infant receives, co-infection with respiratory viruses and perhaps genetic factors related to the pathogen or the infant. The source of pertussis in young infants is usually a household contact (most often the mother) who has a cough illness that is not recognized by physicians or family members as pertussis.

The progression of illness in young infants is related to the risk factors mentioned above.

- Illness onset is often not alarming with the occurrence of coryza and no or minimal fever. This is followed by the onset of cough.
- Cough in young infants is often not recognized as cough, however it is occurring in paroxysms and this may lead to apnea, hypoxia and occasionally seizures.
- The lack of fever and the mildness of initial symptoms often results in clinicians underestimating the potential severity of the illness and this leads to a delay in diagnosis and effective treatment.
- There are no clinical exam findings that help predict which infants will progress to severe, life-threatening disease: all infections in infants, particularly those ≤ 3 months old, should be considered serious until observation while receiving antimicrobial treatment suggests otherwise.
- Initially the chest is clear on auscultation but in fatal cases *B. pertussis* pneumonia is always present.
- Co-infection with respiratory viruses (particularly RSV and adenoviruses) can confuse the diagnoses because of a bronchiolitic picture (air trapping and expiratory distress).

Almost all fatal cases have extreme leukocytosis with lymphocytosis and most will have evidence of pulmonary hypertension.

Pertussis in infants should be diagnosed by culture or PCR on a properly collected nasopharyngeal specimen (swab or aspirate). Also leukocytosis with lymphocytosis (a white blood cell count of $\geq 20,000$ cells/mm³ with $\geq 50\%$ lymphocytes) in any young infant with an illness with cough is a strong indication of *B. pertussis* infection.

If pertussis is a possible diagnosis in a young infant treatment with azithromycin should be started immediately. All young infants (≤ 3 months old) with possible pertussis should be admitted to the hospital and many will require PICU care.

In a review of pertussis deaths in infants < 3 months old in California, it is apparent that the primary care and emergency room physicians underestimated the impending severity of the illness, which delayed hospital admission and contributed to the fatal outcome. Because the severity of illness is unpredictable and clinical decline is often rapid, hospitalization in a major medical center with a PICU is desirable.

It has been observed in numerous small studies that pertussis infant deaths relate directly to the degree of leukocytosis.^{1,2} Based upon this attempts have been made, by double volume exchange transfusion, to lower the white blood cell count. Although no controlled studies have been done, there are a number of experiences in case studies which suggest that exchange transfusion has been useful. However, it must be emphasized that for exchange transfusion to be successful it must be done before the infant is in extreme distress with multiorgan failure.

A total count of $\geq 30,000$ WBCs/mm³ is cause for concern and the rapidity of the WBC count rise is also an important indicator of worsening condition. If white blood cell/lymphocyte counts are increasing, they should be checked every six hours; if stable or decreasing, once a day is sufficient. If pneumonia and rapid pulse (≥ 180) are also present, exchange transfusion should be strongly considered.

Almost all infant deaths over the past 10 years in California have been associated with very high white blood cell counts and *B. pertussis* pneumonia and none were related to irreversible apnea. However, it is possible that deaths related to untreated apnea occur. In infants with pertussis who do not have leukocytosis or pneumonia, the frequency of paroxysms and related apnea decrease sooner than the severity of the events so it is recommended that such infants not be discharged based on the decreased frequency of these events, but rather on the decreased severity of these events.

Specific information relating to pertussis in infants is attached in the appendices:

- I. Laboratory diagnosis of *Bordetella pertussis* infection in infants
- II. Azithromycin treatment of young infants with pertussis
- III. Guidelines for PICU care, including exchange transfusion
- IV. Four pediatric infectious diseases programs that may be called for management advice and decisions (available 24 hours a day). Also listed is one group of intensivists who may be contacted regarding PICU care (available 24 hours a day)

In addition, California Department of Public Health *B. pertussis* laboratory testing recommendations can be accessed at:

<http://www.cdph.ca.gov/programs/immunize/Documents/PertussisLaboratoryTesting.pdf>

Other California Department of Public Health pertussis recommendations can be accessed at:

<http://www.cdph.ca.gov/HealthInfo/discond/Documents/Pertussisquicksheet.pdf>

Appendix I

Laboratory Diagnosis of *Bordetella pertussis* Infection in Infants

In contrast with older children, adolescents and adults the laboratory diagnosis of *B. pertussis* infection in young infants is very sensitive. Young infants tend to have infections with a high concentration of *B. pertussis* in the nasopharynx and this persists for 2 to 6 weeks if untreated.

The California Department of Public Health has recommendations for proper specimen collection for *B. pertussis* culture and PCR testing that can be accessed at:

<http://www.cdph.ca.gov/programs/immunize/Documents/PertussisLaboratoryTesting.pdf>

Please note that serologic testing has no role in the diagnosis of pertussis in young infants.

Also extremely useful in the diagnosis of pertussis in young infants is the presence of marked leukocytosis with lymphocytosis. Although this finding has not been quantitatively evaluated the following guidelines are suggested. A total count of $\geq 20,000$ WBCs/mm³ with $\geq 10,000$ lymphocytes/mm³ in a young infant with coryza, cough, apnea or other respiratory distress is indicative of *B. pertussis* infection. The neutrophilia in pertussis generally occurs without a significant increase in band forms.

Appendix II

Azithromycin Treatment of Young Infants with Pertussis

Although the U.S. Food and Drug Administration (FDA) has not licensed any macrolide for use in infants aged < 6 months the CDC and AAP recommend that azithromycin be used for the treatment of young infants with pertussis and also for the prevention of pertussis in young infants who are exposed to pertussis.³ Azithromycin rather than erythromycin is recommended for young infants because erythromycin is a precipitating factor in infantile hypertrophic pyloric stenosis (IHPS) and it is felt that IHPS is less likely to occur after azithromycin administration.

All infants with suspected pertussis should be treated immediately (do not wait for culture or PCR results) with azithromycin. The dose is 10mg/kg per day in a single dose, each day, for 5 days (do not decrease the dose on day 2, as is routine for otitis media). All treated infants who are \leq 1 month of age should be watched for the development of IHPS. For exposed young infants, azithromycin should be used prophylactically. The dose and duration are the same as for treatment.

Additional California Department of Public Health recommendations for pertussis treatment, can be accessed at: <http://www.cdph.ca.gov/HealthInfo/discond/Documents/Pertussisquicksheet.pdf>

Appendix III

Guidelines for PICU Care

A child with pertussis may require care in the intensive care unit for multiple reasons. Apnea, pneumonia, and seizures are the most common presenting symptoms requiring ICU care. The child with apnea may require mechanical ventilation but has an excellent prognosis for survival. Seizures are treated in the usual manner. The most critically ill children, however, often present with pneumonia and develop refractory hypoxemia, pulmonary hypertension and cardiac failure.

The pulmonary hypertension is related to the hyperleukocytosis frequently found with critical pertussis.^{1,2} The leukocytes aggregate within the pulmonary circulation and form a mechanical obstruction to transpulmonary blood flow with the result being severe hypoxemia and pulmonary hypertension. The pulmonary hypertension is often refractory to nitric oxide and caution should be exercised in its use. *Bordetella pertussis* tracheal cytotoxin leads to injury to the ciliated epithelial cells via induction of nitric oxide synthase.¹ When this induction is blocked, the epithelial cell injury is not seen. Other maneuvers to decrease pulmonary artery pressure may be helpful.

The cardiac failure associated with critical pertussis is likely right sided heart failure secondary to the pulmonary hypertension and left sided failure both from inadequate filling volumes and altered stroke volume secondary to the distended right ventricle and ventricular interdependence. Thus, the pharmacologic management of the resultant low cardiac output state may be less effective than in other low output states.

Multiple authors have reported double volume exchange transfusion as an effective therapy for the pulmonary hypertension, and secondarily the hypoxemia and cardiac failure seen in the most critically ill patients. As the most critically ill patients are typically quite young, the technique of double volume exchange utilized is the same as performed for the newborn with hyperbilirubinemia.⁴

Briefly, the volume of the patient's blood is assumed to be approximately 75- 80 ml/kg body weight. Twice this volume of blood is prepared by the blood bank reconstituted to a hematocrit of approximately 40%. Exchange transfusion trays are available in many neonatal intensive care units and include the necessary stopcocks, syringes and tubing to facilitate the double volume exchange transfusion. In the absence of such a kit, standard stopcocks, syringes, and IV tubing can be utilized.

If an arterial catheter and secure venous catheter are available the patient's blood can be withdrawn from the arterial catheter and simultaneously an aliquot of the prepared blood can be infused via the venous catheter. With the two catheter technique 10 to 30 ml syringes are typically utilized to withdraw and infuse the aliquots. If only a single central catheter is utilized smaller aliquots of 5 to 20 ml syringes are typically utilized during the exchange to avoid significant volume changes, especially in the critically ill infant.

The double volume exchange typically takes approximately an hour to accomplish and care must be taken to insure equal volumes are withdrawn and transfused. A dedicated person should record each aliquot infused and removed and appropriate vital signs. Hypomagnesemia and especially hypocalcemia may occur from binding to the citrate in the transfused blood and some authors recommend routine calcium supplementation.

Following exchange transfusion some patients have a very significant improvement and others continue to deteriorate. Extracorporeal membrane oxygenation (ECMO) has been utilized for patients who remain with intractable respiratory or cardiac failure. The mortality rate for patients with pertussis requiring ECMO approaches 70%, higher than for ECMO performed for other reasons.

Appendix IV

Pediatric infectious diseases programs that may be called 24/7 for pertussis management advice and decisions:

1.) Mattel Children's Hospital Division of Pediatric Infectious Diseases

Call the UCLA Health Systems page operator at 310-825-6301 and ask to speak to the Pediatric Infectious Diseases Fellow on call.

2.) Rady Children's Hospital San Diego/UCSD, Division of Infectious Diseases

Call the Division of Infectious Diseases, Rady Children's Hospital San Diego/UCSD, at 858-966-7785 (direct office number). After hours, the office number will connect you to the on call ID physician pager, or you can reach the on call doctor through the main Rady Children's Hospital operator at 858-576-1700.

3.) UCSF Division of Pediatric Infectious Diseases

Call the UCSF Pediatric Access Center and ask them to reach the Pediatric Infectious Disease Fellow on call. The phone number for the access center is 877-UC Child or 877-822-4453.

4.) Children's Hospital Los Angeles Division of Infectious Disease

Call Children's Hospital Los Angeles Division of Infectious Disease Office 323-361-2509 week days from 8:00 am to 4:30 pm. After hours and on weekends call Children's Hospital Los Angeles operator at 323-361-2450 and ask for the Infectious disease physician on call.

Pediatric intensivists that may be called 24/7 with questions about PICU care:

Rady Children's Hospital San Diego/UCSD, Pediatric Intensive Care Unit

Call 858-966-5900 and ask for the intensivist on call.

References

1. Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to *Bordetella pertussis* and other *Bordetella* subspecies. Clin Microbiol Rev. 2005;18(2):326-82.
2. Paddock CD, Sanden GN, Cherry JD, et. al. Pathology and pathogenesis of fatal *Bordetella pertussis* infection in infants. Clinical Infect Dis. 2008; 328-38.
3. CDC, MMWR. Recommended Antimicrobial Agents for the Treatment and Postexposure Prophylaxis of Pertussis. 2005 CDC Guidelines. 2005;54-RR12:1-16.
4. Chen H, Lee M, Tsao L. Exchange Transfusion Using Peripheral Vessels Is Safe and Effective in Newborn Infants. Pediatrics 2008;122 e1-6. The web address for the free download is: <http://www.pediatrics.org/cgi/content/full/peds.2008-0249v1>